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10/520,883	08/25/2005	Jorg Peters	Le A 36 075	7044

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EXAMINER	
LI, RUIXIANG	
ART UNIT	**PAPER NUMBER**
1646	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,883	PETERS ET AL.	
	Examiner	Art Unit	
	RUIXIANG LI	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,19 and 20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14, 19, and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

Applicant's amendment filed on 11/27/2009 has been entered. Claims 1 and 20 are amended. Claims 1-14, 19, and 20 are pending and under consideration.

Withdrawn Objections and/or Rejections

The rejections of claim 17 under 35 U.S.C. 103(a) as being unpatentable over Domingues et al. (Journal of Biotechnology 84:217-230, 2000) in view of Wyllie et al. (U.S. Patent No. 5,932,102, Aug. 3, 1999) is made moot by canceled claim.

The rejection of claims 15 and 16 under 35 U.S.C. 103(a) as being unpatentable over Domingues et al. (Journal of Biotechnology 84:217-230, 2000) and Wyllie et al. (U.S. Patent No. 5,932,102, Aug. 3, 1999) as applied to claims 1-6, 8, 11, 13, 14, 17, and 19 above, and further in view of US Patent No. 5,739,281 (Apr. 14, 1998) is made moot by canceled claims.

Claim Rejections Under 35 U.S.C. §103 (a)

(i). The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention

was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

(ii). Claims 1-6, 8, 11, 13, 14, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Domingues et al. (Journal of Biotechnology 84:217-230, 2000) in view of Wyllie et al. (U.S. Patent No. 5,932,102, Aug. 3, 1999).

Domingues et al. teach a method for purifying interleukin-4 or mutants by recombinant expression comprising (a) expression in inclusion bodies (page 220, right column, the 3rd paragraph), (b) disrupting the cells and separating the inclusion bodies, (c) washing inclusion bodies obtained with 0.1 M Tris-HCl pH8/1 mM EDTA/0.1% zwittergent, (d) solublizing the inclusion bodies in 8 M GdnHCl, (e) renaturating the expression product and purifying the expression product by cross-flow ultrafiltration against five volumes of buffer (page 220, right column, the 4th paragraph to page 221, the first paragraph of left column).

Domingues et al. fail to teach steps (e) and (f) of claim 1, .i.e., separating the denatured IL-4 or muteins thereof using an immobilized metal chelate affinity chromatography (IMAC) system and releasing the IL-4 or muteins thereof from the IMAC system.

Wyllie et al. teach a method for purifying a protein containing histidine residues using immobilized metal affinity chromatography (Abstract). Wyllie et al. teach that human IL-4 has 5 histidine residues and is predicted to have high affinity to the immobilized metal

(bottom of column 3). Wyllie et al. also teach purifying human IL-4 from E. coli. using Zinc-chelating affinity chromatography (columns 5 to 6).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the method of Domingues et al. to purify the denatured IL-4 or muteins thereof using an immobilized metal chelate affinity chromatography with a reasonable expectation of success. One would have been motivated to do so because an immobilized metal chelate affinity chromatography provides an alternative approach for purifying IL-4 as demonstrated by Wyllie et al. The step of separating the denatured IL-4 or muteins thereof with the IMAC system (Zinc-chelating affinity chromatography) is expected to provide an average recovery of the Il-4 or muteins thereof bettern than 80% and a purity of the IL-4 or muteins thereof of about 90% by SDS-PAGE analysis.

It is also noted that while the cited references do not teach the specific zwitterionic detergents listed in claim 19, it would have been obvious to one having ordinary skill in the art at the time the invention was made to use a zwitterionic detergent, such as CHAPS or zwittergent series, in a washing buffer with a reasonable expectation of success. One would have been motivated to do so because a zwitterionic detergent, such as CHAPS or zwittergent series,has been widely used for such a purpose.

Response to Applicants‘ argument

Citing case law, Applicants argue that the claims are not obvious based on Domingues et al. and Wyllie et al. Applicants argue that the presently claimed purity and recovery are not inherently disclosed by the cited references. Applicants argue that Wyllie et al. do not provide any purity data regarding IL-4, while teaching that IL-4 is quantitatively recovered (>85%) in the elute when located onto zinc-chelating Sepharose at pH7.0, 7.2, or 7.5 and above. Applicants also argue that Wyllie et al. teach that when a relative pure preparation of IL-13 (>80%) was applied to the resin at pH7.5 and eluted with imidazole gradient, recovery was 30% with a purity of >90%. Applicants argue that since the only example in Wyllie et al with purity data actually teaches low recovery with high purity, Wyllie et al. do not teach that IMAC inevitably provides high recovery and high purity of IL-4.

Applicants' argument has been fully considered, but is not deemed to be persuasive for the following reasons. First, Wyllie et al clearly teach that IL-13 did not exhibit high affinity to Zinc-chelating Sepharose and the poor recovery was due to the low affinity to the Zinc-chelating Sepharose (the bottom of column 6 to top of column 7; Table on columns 5 and 6). In contrast, IL-4 exhibited high affinity (column 4, lines 18-22) and was very effectively purified from a crude E. coli broth at several pH conditions (Table on columns 5 and 6; bottom of column 5). Thus, the recovery rate and purity on Zinc-chelating Sepharose vary with proteins.

Secondly, the protein at issue here is IL-4. Since Wyllie et al. teach that human IL-4 could be purified effectively on the Zinc-chelating Sepharose and Zn-chelating chromatography had been utilized in the clinical production of human IL-4 (column 1, last paragrpah), and since the claims do not require any special procedures other than separating IL-4 or muteins thereof using an immobilized metal chelate affinity chromatography system, the human IL-4 purified on the Zinc-chelating Sepharose taught by Wyllie et al is expected and necessarily to have 90% or higher purity.

(iii). Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Domingues et al. (Journal of Biotechnology 84:217-230, 2000) and Wyllie et al. (U.S. Patent No. 5,932,102, Aug. 3, 1999) as applied to claims 1-6, 8, 11, 13, 14, and 19 above, and further in view of Apeler et al. (EP 1022337 A2, 07/26/2000).

Domingues et al. and Wyllie et al. teach a method for purifying interleukin-4 or mutants by recombinant expression using an immobilized metal chelate affinity chromatography as applied to claims 1-6, 8, 11, 13, 14, and 19 above.

Domingues et al. and Wyllie et al. fail to teach a method for purifying an interleukin-4 mutant, Interleukin-4 R121D Y124D.

Apeler et al. teach expression of a human interleukin-4 mutant, Interleukin-4 R121D Y124D (page 2, paragraphs [0002] and [0007]).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to apply the method taught by Domingues et al. and Wyllie et al. to purify interleukin-4 R121D Y124D using an immobilized metal chelate affinity chromatography with a reasonable expectation of success. One would have been motivated to do so because the human interleukin-4 mutants, Interleukin-4 R121D Y124D, comprise 5 histidine residues and would have a high affinity to an immobilized metal as taught by Wyllie et al. (bottom of column 3).

(iv). Claims 9 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Domingues et al. (Journal of Biotechnology 84:217-230, 2000) and Wyllie et al. (U.S. Patent No. 5,932,102, Aug. 3, 1999) as applied to claims 1-6, 8, 11, 13, 14, and 19 above, and further in view of Apeler et al. (EP 1022337 A2, 07/26/2000).

Domingues et al. and Wyllie et al. teach a method for purifying interleukin-4 or mutants by recombinant expression using an immobilized metal chelate affinity chromatography as applied to claims 1-6, 8, 11, 13, 14, and 19 above.

Domingues et al. and Wyllie et al. fail to teach the renaturation of interleukin-4 or mutants by dialysis in the presence of an artificial chaperone.

Gellman et al. teach the use of an artificial chaperone, such as β-cyclodextrin for refolding enzymes (see Example 1).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the method of Domingues et al. and Wyllie et al. to use an artificial chaperone, such as β-cyclodextrin for refolding interleukin-4 or mutants thereof with a reasonable expectation of success. One would have been motivated to do so because an artificial chaperone, such as β-cyclodextrin, causes the detergents to be sequestered from a protein and detergent complex and allows the protein to achieve the correct folding as demonstrated by Gellman et al. (see, e.g, Example 1).

(v). Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Domingues et al. (Journal of Biotechnology 84:217-230, 2000) and Wyllie et al. (U.S. Patent No. 5,932,102, Aug. 3, 1999) as applied to claims 1-6, 8, 11, 13, 14, and 19 above, and further in view of Bonsch et al. (J. Biol. Chem. 270:8452-8457, 1995).

Domingues et al. and Wyllie et al. teach a method for purifying interleukin-4 or mutants by recombinant expression using an immobilized metal chelate affinity chromatography as applied to claims 1-6, 8, 11, 13, 14, and 19 above.

Domingues et al. and Wyllie et al. fail to teach a method for purifying mIL-4 Q116D and Y119D.

Bonsch et al. teach mIL-4 Q116D and Y119D, the murine homologs of human IL-4 R121D and Y124D (Fig. 8; page 8457, right column).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to apply the method taught by Domingues et al. and Wyllie et al. to purify mIL-4 Q116D and Y119D using an immobilized metal chelate affinity chromatography with a reasonable expectation of success. One would have been motivated to do so because mIL-4 Q116D and Y119D, the murine homologs of human IL-4 R121D and Y124D, comprise histidine residues and would have a high affinity to an immobilized metal as taught by Wyllie et al. (bottom of column 3).

(vi). Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Domingues et al. (Journal of Biotechnology 84:217-230, 2000) and Wyllie et al. (U.S. Patent No. 5,932,102, Aug. 3, 1999) as applied to claims 1-6, 8, 11, 13, 14, and 19 above, and further in view of US Patent No. 5,739,281 (Apr. 14, 1998).

Domingues et al. and Wyllie et al. teach a method for purifying interleukin-4 or mutants by recombinant expression using an immobilized metal chelate affinity chromatography as applied to claims 1-6, 8, 11, 13, 14, and 19 above.

Domingues et al. and Wyllie et al. fail to teach renaturing the denatured IL-4 or muteins thereof prior to the step of releasing the Il-4 or muteins thereof from the IMAC system.

US Patent No. 5,739,281 teaches refolding of numerous proteins, including human and murine β2-microglobulin (Example 1) and human growth hormone (Example 2) by a cyclic folding procedure on Ni^{2+} activated NTA-agarose matrix (Ni^{2+}NTA-agarose).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the method of Domingues et al. and Wyllie et al. to use matrix-assisted refolding taught by US Patent No. 5,739,281 wherein the IL-4 remains bound to the IMAC system with a reasonable expectation of success. One would have been motivated to do so because matrix-assisted refolding provides an efficient and alternative approach for refolding of proteins as demonstrated by US Patent No. 5,739,281.

Response to Applicants' argument

With respect to the rejections of claims 7, 9, 10, 12, and 20, Applicants argue that the combination of Domingues et al. and Wyllie et al. does not disclose or even suggest the presently claimed recovery and purity. Applicants argue that combining Domingues et al. and Wyllie et al. with Apeler et al., Gellman et al., Bonsch et al., or Thøgersen (U.S. Patent No. 5739281) does not cure this deficiency because Apeler et al., Gellman et al., Bonsch et al., or Thøgersen are silent regarding IMAC.

Applicants' argument has been fully considered, but is not deemed to be persuasive for the reasons set forth above.

Claim Objection

Claim 20 is objected to because of a typographic error: there are two f) steps in the claim. Correction is required.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruixiang Li whose telephone number is (571) 272-0875. The examiner can normally be reached on Monday through Friday from 8:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached on (571) 272-0835. The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, please contact the Electronic Business Center (EBC) at the toll-free phone number 866-217-9197.

/Ruixiang Li/
Primary Examiner, Art Unit 1646

Ruixiang Li, Ph.D.
January 21, 2010